REMARKS

Claims 51, 53, 54, 56, 59, and 68-77 are pending in this application. Claims 49, 50, 52, 55, 57, 58 and 60-67 have been canceled without prejudice or disclaimer and amendments are proposed to claims 53, 59, 76 and 77 in this Amendment under 37 C.F.R. 1.116.

As a result of the claim amendments, all of the claims are now directed to "determination of malignancy". The claims directed only to measuring the amount of types of thyroglobulin have been canceled.

Support for the amendment to claim 59 (–to an amount of total thyroglobulin in the sample–) may be found in the specification on page 26, lines 19 to 28, and in Example 1 on page 28.

The rejection of claims 49-77 under 35 U.S.C. 112, first paragraph, as not being enabled by the specification, is maintained (Office action point 2).

The rejection is moot for claims 49, 50, 52, 55, 57, 58 and 60-67, which have been canceled without prejudice or disclaimer. The rejection of pending claims 51, 53, 54, 56, 59, and 68-77 is respectfully traversed.

In point a) of the Final Office action, the Examiner states that the claimed methods "only distinguish between one specific subclass of thyroglobulin molecules and fails to differentiate between thyroglobulins which are different "types" but which to not express distinct sugar chains .... The claims ... encompass numerous thyroglobulins which could not necessarily be distinguished by different sugar chains."

Applicants respectfully submit that this comment is unclear and does not appear to be related to enablement. The issue in enablement is only whether one of ordinary skill in the art could carry out the claimed method, and not what might be the scientific meaning of the result of carrying out

the method. That is, even if the Examiner were correct that there were thyroglobulins which could not be distinguished--although Applicants are unclear as to the meaning of this--the claims still define a method which can be carried out by one of ordinary skill in the art.

In point b), the Examiner states that "how medically accurate" does matter for enablement. Applicants respectfully disagree. Enablement involves disclosing an invention so that one skilled in the art can practice it. The present claims are adequately disclosed such that one can easily practice the recited methods and get a defined result. While it may be an issue for, say, the FDA, whether this method may be used medically, this is not an issue with regard to patentability.

Claims 49-66, 68-75 and 77 are rejected under 35 U.S.C. 103(a) as unpatentable over Hanham et al. (Biochemica et Biophysica Acta, Vol. 884, 1986) in view of Voller et al. (Rul. World Health Organ., Vol. 53, pp. 55-65, 1976) or Harlow and Lane (Antibodies, a Laboratory Manual, Chap. 14, pp. 553-612, 1988) or Samuel et al. (U.S. Pat. No. 5,242,799) (Office action point 3).

The rejection is moot for claims 49, 50, 52, 55, 57, 58 and 60-66, which have been canceled without prejudice or disclaimer. Reconsideration of the rejection of pending claims 51, 53, 54, 56, 59, 68-75 and 77 is respectfully requested.

In the final Office action, the Examiner summarizes Applicants' arguments from the previous Response in points a) to e) on page 8 of the Office action, and responds to these on page 9. Applicants here respond to these points.

In point a), the Examiner refers to Applicants' argument that Hanham does not describe adding an antibody or a lectin to a **fluid sample** containing thyroglobulin, as recited in the claims.

The Examiner then proceeds to state that this is not correct because "The antibodies and lectins are added to the fluid sample when the sample is mixed with the gels." Applicants believe that this is an improper semantic argument. A gel is not the same as a fluid sample. A similar argument applies in point b).

Likewise, in point c), the Examiner states that the text "allowing characterization of small quantities of thyroglobulin" makes Hanham a quantitative method. However, Applicants assert that "characterization" means "detection", not "quantitation."

With regard to point d), Applicants continue to assert that Samuel et al. indicates that the lectin must bind to the antigen independently of the antibody, which is inconsistent with those claims in which the antibody will not bind to the thyroglobulin when the lectin is bound. This point is relevant to claims 70, 71, 72 and 75.

The Examiner appears to agree with Applicants' point e), and does not give any additional detail as to how Voller et al. and Harlow and Lane contribute to the rejection.

In addition, Applicants note that all of the pending claims are directed to determination of malignancy, and note the following points about the cited references:

Hanham et al. discloses a procedure in which purified Tg treated with or without enzyme is applied to lectin affinity electrophoresis using agarose gels containing lectin such as ConA, RCA, LCA, etc. only, whereby the sugar chain structure is **identified**. However, this reference does not indicate which sugar chain structure of Tg is characteristic of thyroid tumor. That is, there is no teaching or suggestion of the determination of malignancy of thyroid tumor.

Samuel et al. discloses a detection method of Friedenreich (TF) antigen by antibody/lectin immunoassay using a lectin and an antibody specific to the erythrocyte antigen. However, Samuel

et al. does not mention Tg or its measurement, nor does it mention malignancy.

Voller et al., and Harlow and Lane are merely cited for known quantitative immunoassay methods. They do not disclose or suggest the determination of malignancy of thyroid tumor.

Applicants therefore assert that pending claims 51, 53, 54, 56, 59, 68-75 and 77 are novel and non-obvious over the cited references.

Claims 49-66, 68-75 and 77 are rejected under 35 U.S.C. 103(a) as unpatentable over Heilig et al. (Endocrin. Suppl. 108(267), p. 151, 1985) in view of Voller et al. (Rul. World Health Organ., Vol. 53, pp. 55-65, 1976) or Harlow and Lane (Antibodies, a Laboratory Manual, Chap. 14, pp. 553-612, 1988) or Samuel et al. (U.S. Pat. No. 5,242,799) (Office action point 4).

The rejection is moot for claims 49, 50, 52, 55, 57, 58 and 60-66, which have been canceled without prejudice or disclaimer. Reconsideration of the rejection of pending claims 51, 53, 54, 56, 59, 68-75 and 77 is respectfully requested.

The Examiner reiterates arguments from point 5 of the Office action of August 23, 2001, and now states on page 11 that "Applicant's arguments are not commensurate in scope with the claims." and further states: "... the claims are drawn to detecting any sugar chain variation ...."

Applicants respectfully disagree that their previous comments were not commensurate in scope with the claims. Detecting sugar chain variation may be a result of carrying out the method of some of the claims, but the Examiner's comment does not address the specific recitations of the claims. Applicants' arguments **were** directed to the claim recitations and the specific teachings of the references, and Applicants continue to assert that no *prima facie* case of obviousness can be

made for these claims using these references, as argued in the Response of November 19, 2001, on pages 8-9.

In addition, Applicants note that Heilig et al. does not disclose or suggest the measurement of Tg or determination of malignancy of thyroid tumor, which is the goal of all of the pending claims.

Applicants therefore assert that pending claims 51, 53, 54, 56, 59, 68-75 and 77 are novel and non-obvious over the cited references.

Claims 49-66, 68-75 and 77 are rejected under 35 U.S.C. 103(a) as unpatentable over Wang et al. (Chung-hua Ping Li Hsueh Tsa Chin, vol. 19(2), pp. 90-93) in view of Lo Gerfo et al., (Lancet (1977), vol. 1, No. 8017, pp. 881-882), and further in view of Voller et al. (Rul. World Health Organ., Vol. 53, pp. 55-65, 1976) or Harlow and Lane (Antibodies, a Laboratory Manual, Chap. 14, pp. 553-612, 1988) or Samuel et al. (U.S. Pat. No. 5,242,799) (Office action point 5).

The rejection is moot for claims 49, 50, 52, 55, 57, 58 and 60-66, which have been canceled without prejudice or disclaimer. Reconsideration of the rejection of pending claims 51, 53, 54, 56, 59, 68-75 and 77 is respectfully requested.

The Examiner has repeated the argument of point 6 of the Office action of August 23, 2001, and responds to Applicants' arguments of November 19, 2001, on page 13-14, points a) to e).

Regarding point a), Applicants wish to note that Applicants had never stated that "Wang et al. does not indicate what the lectins binding to the thyroglobulin are." This appears to be a misinterpretation of Applicants' statement that "There is no indication in the abstract as to what

molecules the lectins are binding **to**." (Page 10 of Response of November 19, 2001, emphasis added.)

The Examiner has now provided a copy of the full Wang reference, and Applicants here comment on the teaching of Wang.

With regard to point b, Applicants continue to maintain that Wang does not indicate that lectins are binding to Tg. Applicants had previously stated that Wang had not discussed what molecules the lectins were binding to. The full Wang paper is more specific than the abstract in specifically referring to WGA, PNA, SBA and UEA, and indicating the sugar moieties to which these are specific, in Table 2. However, as noted below, Applicants continue to assert that Wang does not indicate that the lectins are binding to the Tg.

Applicants had previously noted that Wang did not appear to give any data indicating that the lectins might be binding to the Tg, and, based on the full Wang reference, Applicants continue to assert that this is the case. In Wang, Tg binding was 84% of the total samples (Table 3, line 9), while lectin binding was 80% for WGA, 56% for PNA and 61% for SBA (Table 4, line 9). Table 4 only addresses overall lectin binding. No direct correlation data between Tg binding and lectin binding appear to be presented. The paper concludes that "the glycogen on the surface of the malignant tumor cell surface is changed." However, this does **not** address if the glycogen is associated with Tg. There appears to be no mention in the paper that the lectins might be binding to sugars on Tg.

Likewise, with regard to point c), there is no indication of differentiation of different Tg's. With regard to point d), Applicants assert that Wang does not disclose amounts of thyroglobulin.

In addition, Wang's assay would not allow quantitative measurement of the amount of

thyroglobulin present, and Wang does not teach or suggest the Tg measurement using a lectin and the determination of malignancy of thyroid tumor.

Lo Gerfo et al. does not teach or suggest the Tg measurement using a lectin and the measurement of Tg according to a difference in sugar chain structure. Lo Gerfo et al. does not teach the determination of malignancy of thyroid tumor using the amount of Tg obtained by measuring the amount of Tg.

Voller et al., Harlow and Lane, and Samuel et al. do not teach the determination of malignancy of thyroid tumor, as discussed above.

Applicants therefore assert that pending claims 51, 53, 54, 56, 59, 68-75 and 77 are novel and non-obvious over the cited references.

Claims 49, 50, 52, and 57-65 are rejected under 35 U.S.C. 103(a) as unpatentable over Canfield et al. (WO 87/00289) in view of Voller et al. (Rul. World Health Organ., Vol. 53, pp. 55-65, 1976) or Harlow and Lane (Antibodies, a Laboratory Manual, Chap. 14, pp. 553-612, 1988) or Samuel et al. (U.S. Pat. No. 5,242,799) (Office action point 6).

The rejection is moot with regard to claims 49, 50, 52, 57, 58 and 60-65, which have been canceled without prejudice or disclaimer. Reconsideration of the rejection of pending claim 59, in view of the amendment to the claim, is respectfully requested.

Claim 59 has been amended to be directed to determination of malignancy. Applicants note that Canfield (WO '289) discloses a method for determining the presence of a soluble desialylated glycoprotein using a lectin and an antibody (claim 1, etc.), and a method of diagnosing a disease such as choriocarcinoma or hydatidiform mole using the presence of elevated levels of disialylated hCG

(claim 16). The specification of the reference only discloses a method for determining hCG.

That is, Canfield does not teach or suggest the determination of malignancy of thyroid tumor based on the amount of Tg having a specific sugar chain structure. However, claim 59 specifically recites steps directed to measurement of Tg having a specific sugar chain structure in steps (1)(a) to (d), and step (2) is a method step specifically directed to determining malignancy of a thyroid tumor based on a calculated ratio.

Applicants therefore assert that the combination of Canfield with the other references does not teach or suggest the recitation of claim 59 or of the other pending claims.

Claims 49-66, 68-75 and 77 are rejected under 35 U.S.C. 103(a) as unpatentable over Canfield et al. (WO 87/00289) in view of Tarutani et al. (J. Biochemistry, vol. 98(3), 1985) or Wang et al. (Chung-hua Ping Li Hsueh Tsa Chin, vol. 19(2), pp. 90-93), or Heilig et al. (Endocrin. Suppl. 108(267), p. 151, 1985), and further in view of Voller et al. (Rul. World Health Organ., Vol. 53, pp. 55-65, 1976) or Harlow and Lane (Antibodies, a Laboratory Manual, Chap. 14, pp. 553-612, 1988) or Samuel et al. (U.S. Pat. No. 5,242,799) (Office action point 7).

The rejection is moot with regard to claims 49, 50, 52, 55, 57 and 58, which have been canceled without prejudice or disclaimer. Reconsideration of the rejection of claims 51, 53, 54, 56, 59-66, 68-75 and 77 is respectfully requested.

Applicants have discussed above the teachings of Canfield et al., Wang et al., Heilig et al., Voller et al., Harlow and Lane and Samuel et al. In particular, none of these references discloses or suggests using measurements of thyroglobulin for determination of malignancy of thyroid tumor, as

recited in the pending claims.

Tarutani can be taken to suggest that there are two separable types of Tg in a thyroid tumor, and does indicate that the tumor Tg has "an abnormally modified carbohydrate structure, at least in part." However Tarutani does not appear to suggest that there is a relationship between the Tg ratio recited in the present claims and the malignancy of the thyroid tumor. In particular, there is no suggestion that the ratio recited in the present claims should be used in a quantitative manner to determine malignancy.

Claims 49-77 are rejected under 35 U.S.C. 103(a) as unpatentable over Canfield et al. (WO 87/00289) in view of Tarutani et al. (J. Biochemistry, vol. 98(3), 1985) or Wang et al. (Chung-hua Ping Li Hsueh Tsa Chin, vol. 19(2), pp. 90-93), or Hanham et al. (Biochemica et Biophysica Acta, Vol. 884, 1986) or Heilig et al. (Endocrin. Suppl. 108(267), p. 151, 1985), and further in view of Voller et al. (Rul. World Health Organ., Vol. 53, pp. 55-65, 1976) or Harlow and Lane (Antibodies, a Laboratory Manual, Chap. 14, pp. 553-612, 1988) or Samuel et al. (U.S. Pat. No. 5,242,799), and further in view of Larena et al. (Langenbacks Archiv fur Chirurgie, Vol. 381/2, pp. 102-113, 1996) (Office action point 8).

The rejection is moot with regard to claims 49, 50, 52, 55, 57, 58 and 60-67, which have been canceled without prejudice or disclaimer. Reconsideration of the rejection of claims 51, 53, 54, 56, 59, and 68-77 is respectfully requested.

Applicants have discussed above the teaching of Canfield et al., Tarutani et al., Wang et al. Hanham et al., Heilig et al., Voller et al., Harlow and Lane and Samuel et al., arguing that these references, taken in combination, do not suggest the recitations of the pending claims. In particular,

Applicants argue that the references do not suggest the determination of malignancy based on the thyroglobulin ratios recited in the claims.

The Examiner states that "Larena compares levels to total thyroglobulin to Lewis expressing thyroglobulin as well as normal thyroid tissue to cancerous tissue." However, Applicants cannot find a disclosure of Tg in the provided abstract of Larena et al. The abstract mentions thyroid tissue, but does not appear to mention that the blood group antigens being studied are associated with thyroglobulin.

Applicants therefore maintain that Larena does not further suggest the determination of malignancy based on the thyroglobulin ratios recited in the claims, and that the pending claims are novel and non-obvious over these references.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact Applicants' undersigned Agent at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

Attached hereto is a marked-up version of the changes made by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

In the event that this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully Submitted,

ARMSTRONG, WESTERMAN & HATTORI, LLP

Daniel A. Geselowitz, Ph.D.
Agent for Applicants
Reg. No. 42,573

DAG/plb
Atty. Docket No. **990701**
Suite 1000,1725 K Street, N.W.
Washington, D.C. 20006
(202) 659-2930

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PATENT TRADEMARK OFFICE

Enclosures: Version with markings to show changes made
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend claims 53, 59, 76 and 77 as follows:

53. (Amended) A method for determining a malignancy of a thyroid tumor from a fluid sample originating from a living body, the steps comprising:

(1) measuring an amount of one of two types of thyroglobulin in a fluid sample originating from a living body, the steps comprising:

(a) providing a reagent comprising,

~~(1)~~ (i) an anti-thyroglobulin antibody capable of binding to a first type of thyroglobulin and a second type of thyroglobulin,

~~(2)~~ (ii) a specific lectin or a specific antibody capable of binding to a specific structure of a sugar chain of the first type of thyroglobulin but not capable of binding to the sugar chain of the second type of thyroglobulin;

(b) adding to the fluid sample said reagent; and

(c)(i) measuring a total amount of conjugate formed in step (b) of the anti-thyroglobulin antibody with both of the first and second types of thyroglobulin; and

(ii) measuring an amount of conjugate formed in step (b) of said specific lectin or said specific antibody with the first type of thyroglobulin,

(2) determining the malignancy of the thyroid tumor by comparing a calculated ratio of the amount measured in (c)(ii) to the amount of total thyroglobulin measured in (c)(i) in the sample with

a corresponding predetermined ratio from a reference fluid sample originating from a living body having a normal thyroid or a benign thyroid;

wherein the sample is determined to be malignant when the calculated ratio is significantly higher or lower than that of the reference fluid sample of the normal or benign thyroid.

59. (Amended) ~~The method of claim 58, wherein the method further comprises~~ A method for determining malignancy of a thyroid tumor comprising:

(1) measuring an amount of one of two types of thyroglobulin in a fluid sample originating from a living body, the steps comprising:

(a) adding to the sample a specific lectin or a specific antibody capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin but not capable of binding to a sugar chain of a second type of thyroglobulin, to form a conjugate of the specific lectin or the specific antibody with the first type of thyroglobulin;

(b) separating said conjugate from the non-conjugated second type of thyroglobulin;

(c) measuring said conjugate content, for determining the amount of the first type of thyroglobulin; or

(d) measuring an amount of the non-conjugated second type of thyroglobulin.

(2) determining malignancy of the thyroid tumor by comparing a calculated ratio of the ~~amounts~~ amount measured in (c) ~~and~~ or (d) to an amount of total thyroglobulin in the sample with a corresponding predetermined ratio from a reference fluid sample originating from a living body having a normal thyroid or a benign thyroid;

wherein the sample is determined to be malignant when the calculated ratio is significantly

higher or lower than that of the reference fluid sample of the normal or benign thyroid.

76. (Amended) The method of claims 51, 56, 59 and 68-75, wherein said specific antibody is one reactive with an Lewis type sugar chain.

77. (Amended) The method according to claims 51, 56, 59 and 68-75, wherein the sugar chain with the specific structure is one found in thyroglobulin which is produced by a carcinoma cell.